CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020304/S004

MEDICAL REVIEW(S)

DIVISION OF GASTROINTESTINAL AND COAGULATION DRUG PRODUCTS

MEDICAL OFFICER'S REVIEW

NDA No.:	20-304/S-004	AUG 18 1998
Drug:	Trasylol (Aprotinin)	
Sponsor:	Bayer Pharmaceutical Division	
Submission:	Amendment to NDA Supplement 004 Revised Draft Packaging Insert	
Date of Submission:	March 18, 1998	
Medical Reviewer:	Lilia Talarico, M.D.	
Date of Review:	August 10, 1998	

BACKGROUND: On October 10, 1996, the sponsor submitted supplement S-004 to NDA 20-304 for the expansion of the indications of Trasylol from "patients undergoing repeat CABG and high-risk primary CABG" to "all patients undergoing CABG surgery with cardiopulmonary bypass".
The efficacy data from three clinical trials were submitted in support of the indication change:

. Study D91-007: A single-center, randomized, double-blind, placebo-controlled, group comparison pilot study of aprotinin effect on heparin usage and platelet dysfunction during CP bypass.

. Study D91-016: A multi-center, randomized, double-blind, placeb0-controlled comparison study to investigate the efficacy and safety of aprotinin in reducing blood loss and transfusion requirement in patients undergoing primary GABG for myocardial revascularization.

. Study 92-048: A multi-center, randomized, double-blind, placebo-controlled comparison study to investigate the effect of aprotinin on graft patency in patients undergoing primary GABG for myocardial revascularization.

Additional information submitted with NDA 20-304/S-004 included the study report PH 25504: "Retrospective Study of Anaphylaxis on Re-Exposure" which provided a retrospective analysis of the frequency of anaphylactic reactions after repeated administration of aprotinin, and pharmacology data pertaining to the "Mechanism of action of Aprotinin."

The efficacy data from the above studies are summarized below.

Study D91-007: "A single-center, randomized, double-blind, placebo-controlled, group comparison pilot study of aprotinin effect on heparin usage and platelet dysfunction during CP bypass." This study was a clinical trial of 99 patients undergoing primary or repeat cardiac surgery with normothermic or slightly hypothermic CPB for CABG or valve replacement. Two thirds of patients underwent repeat cardiac surgery.

The objectives of the study were: 1) to evaluate the interaction of aprotinin with heparin to determine whether aprotinin is a "heparin sparing" agent in view of the observation that the ACT of patients treated with heparin and aprotinin is prolonged beyond the heparin effect, 2) to evaluate the effect of aprotinin on platelet function, and 3) to evaluate the efficacy parameters of reduction in bleeding and transfusion requirement.
The study showed that aprotinin has no heparin sparing effect and that patients treated with aprotinin should be anticoagulated with heparin at the conventional recommended dose and monitored with laboratory tests performed with reagents not affected by aprotinin.

The high dose aprotinin regimen significantly reduced the percentage of patients who required blood or blood product transfusions as well as the amount of blood required and the volume of the thoracic drainage compared to placebo. The low dose aprotinin regimen significantly reduced the amount of blood transfused and the thoracic drainage.

The results of the part of the study that assessed the activating effect of CPB on platelets and the effect of aprotinin on preserving the platelets function were not available at the time of the NDA supplement submission.

Study D92-016: "A multi-center, randomized, double-blind, placebo-controlled comparison study to investigate the efficacy and safety of aprotinin in reducing blood loss and transfusion requirement in patients undergoing primary GABG for myocardial revascularization." This study was designed to assess the efficacy and safety of three regimens of aprotinin compared to placebo in patients undergoing primary CABG. The clinical trial enrolled 704 patients (603 M and 101 F) mainly at 16 US centers. Patients were randomized to four groups, three aprotinin groups and one placebo group. The aprotinin groups included the high-dose (HD) or "full Hammersmith regimen", the low-dose (LD) or "half Hammersmith regimen", and the "Pump Prime Only" (PPO) regimen where aprotinin was administered without loading dose. The randomization was stratified according to the perceived risk of peri-operative MI or bleeding.

The primary efficacy was assessed in terms of reduction of donor blood transfusion requirement up to 12 days post-operatively (number of units of blood or RBC required per patients and percent of patients requiring donor blood transfusions). Secondary efficacy criteria included the number of units of blood transfused, the thoracic drainage rate over 6 hours postoperatively and until drainage removal, re-operation due to bleeding, number of units of blood products (whole blood, RPC, plasma, platelets, cryoprecipitate) up to day 12 post-op and throughout hospitalization.

Safety was assessed by clinical and laboratory parameters. Parameters of MI including all ECG, SGOT, LDH, CK/MB values were reviewed blindly by a Core Laboratory.

Sample size estimation was based on the expected average transfusion requirement of 2.1 units of blood for the placebo patients and on a clinically meaningful reduction of 1 unit of blood for the HD group.

All active treatment groups required significantly less units of donor blood compared to the placebo group and significantly fewer patients in all active treatment groups required donor blood than placebo patients. In the assessment of thoracic drainage, all active treatment groups were superior to placebo for the perioperative and total postoperative period.

Approximately 25% of patients randomized to each group were assessed as low risk of bleeding. In this subgroup, no statistically significant difference was noted among groups for

percentage of patients requiring transfusion and only in the LD group a statistically significant difference was noted for units of blood transfusions required.

The occurrence of death and serious adverse events was similar in all study groups. The incidence of MI was similar in all groups, only a trend in favor of placebo over active treatment was observed in the subset of patients at high risk of MI.

Study D92-048: A multi-center, randomized, double-blind, placebo-controlled comparison study to investigate the effect of aprotinin on graft patency in patients undergoing primary GABG for myocardial revascularization. This study was designed and powered primarily as a safety study to compare the incidence rates of angiographically assessed graft closure in patients undergoing primary CABG receiving either high dose regimen of aprotinin or placebo. A total of 873 patients were enrolled in the study. The study was designed to test for equivalence of incidence of SVG closure for the two groups (95% CI of aprotinin minus placebo difference in percent). The sample size was calculated based on an historically expected rate of graft closure of approximately 15% reported in the medical literature (Goldman S. et al, Circulation, Vol 84, N0 2, August 1991).

An overall greater incidence of graft closure was observed in the aprotinin group compared to the placebo group in both by-patient (15.4% vs 10.9%, p=0.035) and by-graft (7.6% vs 4.7%) analyses. A considerable by-center variation was observed; when only the US centers (54% of the total study population) were analyzed, there was no statistically significant difference in graft closure rates in aprotinin-treated patients (9.4%) vs. placebo (9.5%). Similar results were obtained when by-graft analyses were performed for the US population.

The incidence rates of MI and death were not different in the aprotinin-treated and placebo groups (2.9% vs. 3.8% and 1.4% vs. 1.6% for MI and death respectively).

The efficacy results assessed for the entire study population showed a statistically significant difference in favor of aprotinin treatment for the percentage of patients requiring transfusion of blood or blood product. The statistically significant difference was observed in both high risk and low risk of bleeding patient subgroups.

STUDY REPORT PH 25504: This was a retrospective study of 387 European patients with at least 2 documented Trasylol exposures. The objectives of the study were: 1) to assess the incidence of anaphylactic reactions upon re-exposure to aprotinin; 2) to evaluate the relationship between the time interval between aprotinin exposures and the incidence of anaphylaxis; and 3) to determine the relationship of HI and H2 receptor blockade to the incidence of anaphylaxis in these patients.

A total of 252 adults (age $\geq$ 12 years) and 135 children (age < 12 years) were included in the study, of these, 381 patients with 412 re-exposures were valid for analysis. Thirteen adults and 15 children had 3 exposures to Trasylol. A variety of dosage ranges of aprotinin were used. Histamine blockade was used in 65% of patients; in 92% of them, this included both H1 and H2 blockade

Anaphylactic/anaphylactoid reaction occurred in 11 patients: 1 was life-threatening, 6 were severe, 2 were mild, and 2 were not graded. Combined histamine blockade was given to 8 patients (4 severe, 2 mild, and 2 not graded). A test dose was given prior to surgery in 3 patients, 2 of them reacted to the initial dose. Eight of the 11 patients had an uneventful postoperative course, 1 had delayed recovery, and 2 patients died.

The incidence of anaphylaxis per re-exposure was 2.7% and 2.9% on a per patient basis. The incidence among adults was 3.6%, while for children was 1.5%. A total of 82% of the reactions occurred on re-exposure within 6 months, and 50% of the reactions occurred when the exposure time was less than 2 months. Thus, the incidence rate of anaphylaxis upon re-exposure within 6 months was 5.0% per re-exposure, or 5.2% per patient; the incidence of reactions on re-exposure after 6 months was 0.9% per re-exposure, or 0.91% per patient.

Multiple exposures (>2) increased the risk further. Of 31 patients with multiple exposures (12 with a < 6 month interval between doses), 3 (9.7%) had anaphylactic reactions. All three had an interval of only 3-5 weeks between the last two exposures. Thus, among the 12 patients at highest risk due to multiple exposure with <6 month interval between doses, 25% had anaphylactic reactions.

Aprotinin is a small basic polypeptide of non-human source with relatively weak immunogenicity in humans. Aprotinin can, however induce specific antibodies responsible for anaphylactic reactions upon re-exposure. No IgE specific antibodies in aprotinin

treated patients are found up to 6-7 months post exposure; however IgG anti-aprotinin antibodies at 6-7 months are found in nearly half of patients. The incidence of anaphylaxis is influenced by the total number of exposures to aprotinin and the time from last exposure. Whereas the overall incidence of hypersensitivity to aprotinin (regardless of number of exposures) ranges from anaphylaxis has been observed in about 5% of aprotinin re-exposed patients.

MECHANISM OF ACTION OF APROTININ: A detailed description of the recent advances in the understanding of the mechanisms of action of aprotinin was provided by the sponsor as part of the NDA 20-304/S-004 to address the proposed revisions in the CLINICAL PHARMACOLOGY section of the aprotinin package insert. The information was reviewed, however it was not addressed in the medical review of 1-3-1997.

Recent studies have elucidate some aspect of the complex pathophysiologic changes related to cardiopulmonary bypass (CPB) and have increased the understanding of the mechanism of action of aprotinin.

CPB is associated with a systemic inflammatory response (SIR) whose manifestations range from mild organ dysfunction to multisystem organ failure. Common disturbances associated with CPB include coagulation disorders, platelet defects, plasmin activation, and pulmonary dysfunction as a result of neutrophil sequestration and degranulation resulting in lung injury.

Contact of blood with the non endothelial surfaces of the bypass unit, as well as other events, including activation of the contact activation system, surgical trauma, and lung reperfusion injury, result in increased capillary permeability, contraction of smooth muscle, neutrophil chemotaxis and activation, and ultimately tissue damage.

The multisystem damage is due to inflammatory mediators (including complement anaphylatoxins, kinins, kallikrein, and a variety of cytokines) released during or after CPB. Key among these is kallikrein, which not only initiates the several component cascades (coagulation, complement, kinins) of the contact activation system, but also directly activates both plasmin and neutrophils. SIR is thought to represent a panendothelial cell injury.

Aprotinin is a serine protease inhibitor that inhibits plasmin both directly and indirectly through kallikrein inhibition. Aprotinin inhibits the systemic inflammatory response associated with CPB because the inhibition of kallikrein also results in suppression of a variety of systems involved in the inflammatory response: factor XII, bradykinin, C5a, neutrophil integrin expression and esterase activity, and airway nitric oxide (NO) production. Inhibition of SIR results in reduction in capillary leak, preservation of systemic vascular resistance and blood pressure, and improved myocardial recovery following ischemia.

On August 5, 1998, a non approvable letter for NDA 20-304/S-004 was sent to the sponsor. The expansion of the indication of aprotinin to all CABG patients was not approved based on the following observations:

1) In the pivotal study D92-016, statistically significant efficacy for patients at low risk of bleeding was found only in the LD group and only with respect to units or volume of donor blood transfused. In addition, more than 25% of low-risk patients were enrolled at one center which showed a larger treatment effect than all other centers combined.

2) The risk of allergic/anaphylactic reactions to aprotinin and the increased risk of allergic/anaphylactic reactions on re-exposure to aprotinin limited the benefit of the treatment in patients who were not at high risk of bleeding when undergoing primary CABG surgery while increased the risk of adverse reactions at the time of increased risk of bleeding and greater need for aprotinin therapy if repeated CABG was required.

3) study 92-048 showed efficacy of aprotinin in low bleeding risk patients, however, only the HD was used in this clinical trial.

It was concluded that the benefit to patients with low risk of bleeding did not outweigh the risk of serious allergic reactions to aprotinin, particularly when re-administered.

On August 15, 1997, the sponsor notified the Agency of the intention to amend the supplement 004. On November 10, 1997, the sponsor requested a meeting with the Agency to discuss the following labeling issues:

- Expansion of the indication to all patients undergoing CABG,
- Clinical Trials section of the package insert,
- Agency's concerns of anaphylaxis upon re-exposure to aprotinin,
- Proposed revisions of the CLINICAL PHARMACOLOGY, Mechanism of action section of the package insert.

On January 22, 1998, a meeting was held to discuss the expansion of the indication of aprotinin to include all patients undergoing CABG, the concerns relative to anaphylaxis upon re-exposure to aprotinin, the revisions of the CLINICAL TRIAL section of the labeling and the revision of the CLINICAL PHARMACOLOGY section of the labeling to include data on the mechanism of action of aprotinin.

In support of the clinical rationale for the expansion of the indication to include low-risk primary CABG, the sponsor presented a re-analysis of data from study D92-048 pertaining to the subset of patients at low risk of bleeding and data from two ex-US studies, SN 0406 and SN 0407, that were originally included in the NDA 20-304.

The issues discussed at the January 22, 1998 meeting and the data presented are summarized below.

Re-evaluation of the efficacy data from study D92-048: Because of the adequacy of the study size and statistical power, the efficacy data from the US and non-US study sites were re-evaluated as two pivotal trials. A total of 189 patients from the 471 patients at US sites and 197 patients from the 399 patients enrolled at non-US sites were classified as low risk of bleeding (no history of aspirin for the past 5 days). The patient population undergoing primary CABG with low risk of bleeding included 84 aprotinin and 85 placebo treated evaluable patients from the US sites and 105 aprotinin and 112 placebo treated patients from the non-US sites.
The efficacy results for these population subsets are summarized in the following table.

Table 1: Low-risk CABG efficacy data (Study D92-048)

	Total			US Centers			Non-US Centers		
Parameter	Placebo	Aprotin (H-D)	p-value	Placebo	Aprotin (H-D)	P-value	Placebo	Aprotin (H-D)	p-value
Patients per Group	197	189		85	84		112	105	
Patients requiring any blood	102	66		26	11	P=0.006	76	55	P=0.001
% patients requiring any blood	52	35	P<0.05	31	13	P=0.006	68	52	P=0.001
Mean blood required (mL)				248	74	P=0.003	912	467	P<0.001

Ex-US studies SN 0406 and SN-0407 were both randomized, placebo-controlled, double-blind, single-center studies of patients undergoing primary CABG with low risk of bleeding as patients receiving ASA or other drugs that affect platelet function were excludes from study participation. In both studies, aprotinin was administered at the high-dose regimen.
In both studies, primary efficacy variables were mean total thoracic drainage.

The results of the primary efficacy outcome are summarized in the following table.

Table 2: Efficacy results in primary low-risk CABG

Study Number	SN-0406			SN-0407		
Parameter	Placebo	Aprotinin (H-D)	p-value	Placebo	Aprotinin (H-D)	P-value
Patients per Group	37	40		38	37	
Patients requiring any blood (n)	35	8	P<0.001	25	8	P=<0.001
Patients requiring any blood (%)	95	20	P<0.001	66	22	P=<0.001
Blood required (Mean: mL)	790	576		600	375	P=0.067
Mean Thoracic Drainage	573	309	P<0.01	447	338	P=<0.001
ASA Use	6 weeks	6 weeks		10 days	10 days	

The risk of anaphylaxis on re-exposure to aprotinin and the rationale for the aprotinin warning labeling. The results of the Study Report PH 25504 ("Retrospective Study of Anaphylaxis on Re-Exposure") were presented by the sponsor. The study was a retrospective analysis to determine the frequency of anaphylactic reactions after a second administration of aprotinin. A total of 387 patients with a total of 421 re-exposed to aprotinin were identified. Two thirds of the children were pretreated with

corticosteroids and two thirds of the adults received H1/H2-blockers. Nine cases of allergic/anaphylactic reaction and two less defined reactions were reported: one patient had anaphylactic shock, six experienced circulatory failure. Two patients died. The frequency of reactions was 2.8%. For 9 of the 11 patients with a reaction, the time between the two consecutive exposures was less than 6 months; for one patient, the interval was close to three years. The frequency of reactions for the 173 patients with a re-exposure interval greater than two days and less than 6 months was 5.2% (9/173). Similar incidence of anaphylaxis on re-exposure to aprotinin was reported in two other studies.
The frequency of reactions for the 221 patients with a re-exposure interval greater than 6 months was 0.91% (2/221). The data indicated that the risk of allergic/anaphylactic reactions is higher within the first 6 months than at a later time, more frequent in adults than in children (3.6% vs. 1.5%) and more frequent in females than in males (4.0% vs. 2.4%).

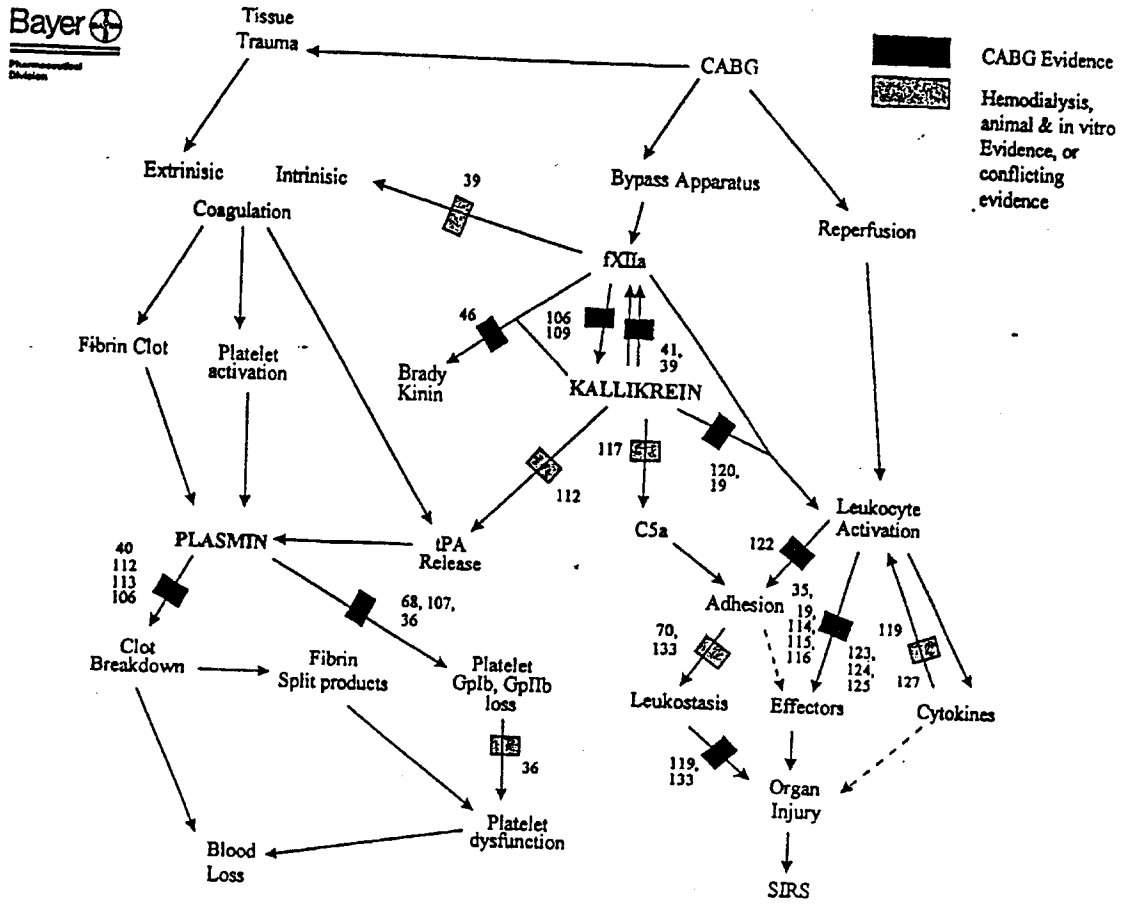
The data from different studies are summarized in the following table.

Risk of Anaphylaxis upon Re-exposure to Aprotinin

Study Study	Number of Patients	Number of RE-Exposures	% anaphylaxis per patient	% anaphylaxis per re-exposure
PH 25504	381	412	2.9	2.7
Shultze Et al	86	ND	5.8	ND
Goldstein Et al	23	ND	4.3	ND
Bayer 0477	102	110	2.9	2.7

Mechanism of Action of Aprotinin: The sponsor presented an overview of the pathogenetic mechanisms involved in the development of systemic inflammatory reactions (SIRS) from exposure of blood to non-endothelialized surfaces (trauma, CPB, hemodialysis) and described the mechanism of action of aprotinin.

These are summarized in the following scheme.



During the meeting, and in the course of the discussion of the mechanism of action of aprotinin, additional questions were raised about the PK and PD interactions of aprotinin and protamine sulfate and the possible relationship between heparin-induced thrombocytopenia (HIT) and thromboembolic complications associated with CABG and the role of aprotinin in the presence of HIT. These issues were considered to be of scientific interest and clinically relevant, however, no data were available.

Comments

The sponsor has provided data from three studies that demonstrate the efficacy of aprotinin compared to placebo in reducing donor blood transfusion requirements in patients undergoing primary CABG in the absence of known risk factors for bleeding.

In all three studies, aprotinin significantly reduced the number of patients requiring donor blood transfusion. In two of the three studies, the amount of blood transfused was significantly less in the aprotinin group.

The data support the proposed expansion of the indication to all patients undergoing CABG surgery. It must be noted, however, that in three studies aprotinin was used at the high dose regimen. The study that evaluated both low and high dose against placebo showed that both doses were equally effective. Therefore it is still unclear whether patients undergoing primary CABG with no known risks of bleeding should receive the low dose regimen. The revised labeling proposed by the sponsor shows the results of the efficacy variables according to aprotinin regimen compared to placebo in the repeat CABG patients and in the primary CABG patients. Both tables of efficacy variables indicate that the difference in efficacy between the high and the low aprotinin dose regimens is not significant.

No significant difference in safety analyses was observed between high dose or low dose regimens. However, the comparison of safety for the two regimens has included only relatively small study populations. A post-marketing analysis of safety in relation to dose regimen used would be very informative.

The sponsor has included the new information pertaining the mechanism of action of aprotinin in the CLINICAL PHARMACOLOGY section of the revised labeling. The information is acceptable, however, the statement that the reduction in inflammatory response by aprotinin translates into improved patient (clinical) outcome is unsubstantiated. The only claim is decreased need for donor blood transfusion.

The two tables of the efficacy variables indicate in a footnote that no statistically significant difference in efficacy or safety have been noted between regimen A (high-dose) or B (low-dose). In addition, the ** referenced footnote also states that reduction in inflammation may only occur at the high dose. This latter statement is unsubstantiated and could encourage the use of high-dose aprotinin without any evidence of additional clinical benefit from the reduction of inflammation.

Interaction between aprotinin and protamine and between aprotinin and possible heparin-induced thrombocytopenia, particularly in terms of adverse events, could be of significant clinical relevance. The sponsor should consider evaluating any interaction between aprotinin and protamine and the possible role

of heparin-induced thrombocytopenia in the development of graft closure and clinically relevant coronary thrombosis in aprotinin treated patients compared to placebo controls.

The sponsor has included a boxed warning to address the risk of anaphylaxis as requested at the January meeting. The information concerns mainly the risk associated with re-exposure to the drug.

REGULATORY RECOMMENDATIONS:

The expansion of the indication for aprotinin to all patients undergoing CABG surgery can be approved.

The sponsor should be requested to revise the labeling as follows:

Aside from labeling requirements, the sponsor should be requested to commit to a postmarketing evaluation and analysis of all reported adverse events by the dose regimen of aprotinin used, i.e., high-dose vs low-dose regimen.

APPEARS THIS WAY
ON ORIGINAL

/S/

Lilia Talarico, M.D.

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NDA 20-304
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DIVISION OF GASTROINTESTINAL AND COAGULATION DRUG PRODUCTS

MEDICAL OFFICER' REVIEW

NDA No.:	20-304 JAN - 8 1997
Drug:	Trasylol (Aprotinin)
Sponsor:	Bayer Pharmaceutical Division
Submission:	NDA Supplement 004: Labeling
Date of Submission:	10-31-1996
Medical Reviewer:	Lilia Talarico, M.D.
Date of Review:	1-3-1997

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OVERALL BACKGROUND INFORMATION

Aprotinin is a single chain polypeptide of MW of 6,512 daltons isolated from bovine lung tissues. Aprotinin is an inhibitor of certain serine proteases including trypsin, plasmin, and plasma and tissue kallikrein.

Aprotinin was evaluated in clinical trials in patients undergoing cardiac surgery with cardiopulmonary bypass (CPB) for valve replacement and for primary or secondary coronary artery bypass surgery (CABG). The following dose regimens of Trasylol have been evaluated in comparison to placebo:

!) High dose (HD) regimen consisting of an intravenous loading dose of Trasylol 280 mg followed by a continuous infusion of 70 mg/hr, plus 280 mg added to the CPB circuit prime.
2) Low Dose (LD) regimen consisting of an intravenous loading dose of Trasylol 140 mg followed by a continuous infusion of 35 mg/hr, plus a dose of 140 mg added to the CPB circuit prime.
3) Pump Prime Only dose (PPO) regimen consisting a placebo bolus and infusion and Trasylol 280 mg added to the CPB circuit prime.
4) The placebo groups received placebo bolus, infusion and CPB circuit prime.

Aprotinin (Trasylol TM) was approved on 12-29-1993 for prophylactic use to reduce perioperative blood loss and transfusion requirement in patients undergoing cardiopulmonary bypass for repeat CABG surgery and in selected cases of primary CABG surgery at high risk of bleeding or when transfusion is unavailable or unacceptable.

The safety concerns raised with the use of Trasylol in CABG surgery (and described in the approved package insert as of 10-12-1994) included the risk of renal dysfunction, the risk of anaphylaxis (particularly of re-exposure to the drug), and the trend toward increased incidence of myocardial infarction (MI) and graft closure.

The sponsor has submitted an NDA supplement with additional data on the efficacy and safety of Trasylol in patients undergoing CABG surgery from three new clinical trials and from a

retrospective review of patients re-exposed to aprotinin. The information is provided in support of proposed revisions in both content and format of the Trasylol labeling. The changes proposed apply to the CLINICAL TRIALS, WARNING, ADVERSE REACTIONS and INDICATIONS sections of the current Trasylol labeling.

The proposed revision of the INDICATION section consists in the broadening of the indications from repeat CABG and high-risk primary CABG patients to include all CABG patients based on the data from the following three new studies:

D91-007: "A Pilot Study of Aprotinin Prevention of Platelet Dysfunction During Ardiopulmonary Bypass".

D92-016: "A Multicenter, Randomized, Double-Blind, Placebo-Controlled Group Comparison Study to Investigate the Efficacy and Safety of Aprotinin in Reducing Blood Loss and Transfusion Requirement in Patients Undergoing Primary Cardiopulmonary Bypass Graft Surgery for Myocardial revascularization (CABG)."

D92-048: "A Multi-center Randomized Double-blind, Placebo-controlled Group comparison Study to Investigate the effect of Aprotinin on Graft Patency in Patients Undergoing Primary Coronary Bypass Surgery (CABG) for Myocardial Revascularization".

The proposed revision of the ADVERSE REACTIONS section consist in the insertion of subsections on Myocardial Infarction and Graft Patency based on data from Study D92-048.

The proposed revision of the WARNINGS section consist of expansion of the section to include information on the risk of anaphylaxis on re-exposure to Trasylol derived from a retrospective review of case studies.

Studies D91-007, D92-048, D92-048 and of PH 25504 (Antigenicity of Trasylol on re-exposure will be reviewed individually.